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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,204	07/18/2001	Avi Ashkenazi	10466/118	1632

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	11

DATE MAILED: 09/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,204	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed 07/18/01 and 8/27/02 have been entered.

Specification

The disclosure is objected to because of the following informalities: on page 202, line 37, "Pro317" should be "PRO317".

Additionally, Applicants are advised that the ATCC has moved from Rockville, MD to Manassas, VA, effective March 23, 1998. The correct address is now:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

The specification should be amended to reflect the correct address for the ATCC. See p. 250, lines 1-2.

Appropriate correction is required.

Sequences

The CRF submitted 01/17/02 has been entered with the following correction made by the USPTO STIC staff: for SEQ ID NO:173, a correction to a nucleic acid number at the end of a nucleic acid line has been made. Notice of this correction is provided for Applicant's information, and no action by Applicant is necessary.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-44, 47, 48, 52, 53 and dependent claims 45, 46, 49-51 and 54-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For claims 39-44, 47, 48, 52 The protein identified as PRO339 is not disclosed as being expressed on a cell surface. Further, it is disclosed as having homology to fringe (p. 34, lines 5-

6), which is a secreted polypeptide necessarily lacking an extracellular domain (Fleming et al., Dev., 124:2973, 1997, p.2974, second sentence of second paragraph). Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 39, parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 39, part (d), for example) is indefinite because a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Claims 52 and 53 are indefinite because the metes and bounds of the claims are not clear. For claim 52 it is not clear if hybridization under any condition is permissible, even the most permissive, allowing non-specific hybridization to occur. For claim 53, while the skilled artisan understands the general concept of hybridization under "stringent conditions", what specific conditions are intended by the use of the term "stringent" in the present claims is unknown. What conditions of stringency are used in any particular situation are determined by the specificity of hybridization desired by the practitioner. The instant specification presents examples but not a limiting definition of "stringent conditions" (p. 74, lines 4-14). In this case, the desired specificity is unknown. "Stringent" carries a meaning of "constricted", implying that not all hybridization conditions are acceptable. If however, there is a structural relatedness (limitation) that is being defined by the conditions, then those conditions or range of conditions must be clear in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-58 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to a nucleic acid encoding a polypeptide comprising the sequence of SEQ ID NO:339 (PRO339) or structurally related polypeptide (*e.g.*, 80% identical to SEQ ID

NO:339) or structurally related nucleic acid (one that hybridizes). With claims drawn to a nucleic acid not identical to SEQ ID NO:338, inclusion of % identity in the claims to a nucleic acid that *encodes* an amino acid sequence (*e.g.*, claim 39(a)), the claim encompasses having the specified % identity to a degenerate sequence encoding SEQ ID NO:339, meaning that the shared structural identity of the claimed sequence to SEQ ID NO:338 can be very low. In the instant specification, it is stated that PRO339 has homology to fringe, a protein involved in development (p. 34, first paragraph). The level of homology is not disclosed. It is also stated that PRO339 has homology to *C. elegans* proteins and collagen-like polymer sequences. The level of homology is not disclosed in the specification. Sequence search results attached entitled "COMPARISONS" show that there is no more than 2.8% identity between SEQ ID NO:339 and prior art fringe proteins (see attached). For *C. elegans* proteins, no more than 15.5% identity was found (see attached), however, the function of the *C. elegans* protein was unknown. No identity between SEQ ID NO:339 and collagen-like polymers could be identified by the examiner. On the basis of homology, it is suggested in the specification that "PRO339 may be involved in development and tissue growth." (p. 191, lines 11-13) How PRO339 is involved in development or tissue growth is not disclosed. Nor does the prior art provide guidance to allow the skilled artisan to use the claimed nucleic acids or encoded polypeptides. None of the sequences sharing sequence identity have a specific or substantial utility. Fringe as discussed by Fleming et al. (*ibid.*) is shown to interact with serrate in drosophila. Wu et al. (Curr. Opin. Neurobiol. 1999 Oct., 9(5):537) say (abstract), "In vertebrates, fringe genes play roles in the formation of apical ectodermal ridge, the dorsal/ventral border in the limb bud, and in the development of somatic borders..... Genetic evidences suggest that Fringe protein functions by modulating the Notch signaling pathway, perhaps through differential regulation of Notch activation by different ligands; however, the mechanism underlying Fringe function remains to be investigated." The instant specification does not assert any specific functions particular to fringe that might be supported by the prior art and would reasonably be expected to be shared by PRO339. Even if there was a known specific and substantial function of *C. elegans* proteins, fringe proteins or collagen-like polymers, and if such function was disclosed in the specification, the low sequence identity shared between those proteins or polymers and SEQ ID NO:339 would not be sufficient to support any common function because of the lack of function/structure relationship within one

of the families that would make it more likely than not that PRO339 possessed any one specific and substantial utility of the prior art proteins.

The specification asserts another utility for PRO339 and its encoding nucleic acid (p. 235, lines 2-3): that it is "likely associated with tumor formation and/or growth". This assertion is based on gene amplification expression experiments in colon and lung tumor cell lines and primary cell cultures (p. 225 and 230-235). From Table 9 it appears there was approximately 2-3 fold amplification (about 1 PCR cycle) in 8 or 17 lung tumor primary cell cultures. There is no specific information on what type of the normal tissue was used as a control and how many normals there were. A single normal sample is not sufficient for basing relative levels of many other samples. Even *if* the data demonstrated a slight increase in copy number of PRO339 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO339 and its encoding nucleic acid can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO339 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

Because it is not know specifically what the functional properties of the polypeptide encoded by the claimed nucleic acid are or what specific properties aside from sequence (*e.g.*, differential expression) the claimed nucleic acid has, the claimed invention is not supported by a specific or well established utility.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-58 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The specification provides little beyond structural data and potential activities of the PRO339 polypeptide without guidance about which specific activities one could reasonably expect the polypeptide or encoding nucleic acid to possess as discussed above. Therefore, it would require undue experimentation to use the claimed invention.

Claims 39-43 and 52-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid encoding a polypeptide having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence or to a nucleic acid that hybridizes to SEQ ID NO:338. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification

does not provide adequate written description of the claimed genus. Which nucleic acids of the genus comprising the required sequence are part of the invention has not been set forth.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising SEQ ID NO:338 or encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:339, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

35 U.S.C. §§ 102 and 103

The following rejections under 35 U.S.C. §§ 102 and 103 are made under the assumption that the effective filing date for the instantly claimed invention is 07/11/2001, which is the actual filing date of the instant application. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. §120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the new claimed invention. Because the

instant application does *not* meet the requirements of 35 U.S.C. § 112, first paragraph, for the reasons given above and it is a continuing application of Serial Number 09/665,350, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-44, 47, 49 and 52-58 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. AB037823 as evidenced by Stratagene Cloning Systems catolog (1994).

GenBank Accession No. AB037823 provides a written description of the claimed nucleic acid (see attached "Sequence Comparison-GenBank"). Under "FEATURES" in the section entitled "source", it is taught that the nucleic acid is in pBluescriptII SK plus" vector. Due to the requirements of sequencing, the nucleic acid was necessarily amplified in a vector in a host cell.

Stratagene Cloning Systems catalog (p. 28-29) teaches that the host for pBluescriptII SK plus is an *E. coli* host. Vector amplification must occur in a host cell. Absent evidence to the contrary, the host cell used for amplification of GenBank Accession No. AB037823 was *E. coli*.

Claims 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,695,995.

US Patent 5,695,995 teach a nucleic acid of SEQ ID NO:16 that would hybridize to SEQ ID NO:338 of the instant application and is at least 10 nucleotides in length.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. AB037823 in view of Applicants' Admission on p. 34, lines 5-6, and Fleming et al. (Dev., 124:2973-81, 1997)

The disclosure of GenBank Accession No. AB037823 is discussed above. GenBank Accession No. AB037823 does not teach a nucleic acid encoding a polypeptide lacking its signal peptide.

Applicants admit (p. 34, lines 5-6) in the instant specification that disclosed PRO339 polypeptide has homology to fringe. Therefore, the polypeptide encoded by GenBank Accession No. AB037823 necessarily shares homology with fringe.

Fleming et al. teach that fringe is a secreted polypeptide, necessarily lacking an associated signal peptide when secreted (Fleming et al, , p.2974, second sentence of second paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid of GenBank Accession No. AB037823 so its encoded protein lacked its associated signal peptide in order to produce a mature secreted active form of the protein in view of the amino acid sequence's relationship to fringe asserted by Applicants, which is a secreted protein. One would have been motivated to produce a mature form since Fleming et al. discuss the secreted form of fringe having developmental activity.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Nagase et al. (DNA Res. 7 :65-73, 2000) teach the isolation and analysis of GenBank Accession No. AB037823 (K1AAA1402 protein). WO200153312 teaches polypeptide SEQ ID NO :2926 as shown on the summary sheet provided and labeled "WO200153312 Comparison" which is identical to SEQ ID NO:339 of the instant application. This publication has not been furnished in whole due to the length of over 10,000 pages. WO200153312 could serve as a reference under 102(e) and would be cumulative with the references relied on above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. Kaufman

Patent Examiner, Art Unit 1646

September 26, 2002